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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants:	Chappel, R. *et al.*	Examiner:	Hines, J.
Serial No:	09/380,826	Art Unit:	1645
Filed:	November 22, 1999	Docket:	DAVIE79.001A
For:	Leptospira pathogens		

EXHIBIT C

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DECLARATION OF RODERICK CHAPPEL
PURSUANT TO 37 C.F.R. §1.132

I, Roderick CHAPPEL, hereby declare as follows:

1. I make this Declaration in support of the above-captioned USSN 09/380,826 (hereinafter referred to as "the present application").

2. I am a citizen of Australia residing at 11 Hillcrest road, Hurstbridge, Victoria 3099, Australia.

3. I am the inventor of the present application and I am fully aware of the subject matter described therein.

4. I am currently employed as a Quality Manager at National Serology Reference Laboratory, Australia, located at 4th Floor, Healy Building, 41 Victoria Parade, Fitzroy, Victoria 3065, Australia. My *curriculum vitae* is affixed hereto as Exhibit I.

5. I have reviewed the March 28, 2001 Office Action, and the references cited therein.

6. At paragraph 7 of the Office Action, the Examiner has rejected claims 2, 19, and 20 under 35 USC 112, first paragraph, as containing subject matter which was not described in the present application in such a way as to reasonably convey to one skilled in the art that the inventor, at the time the application was filed, had possession of the claimed invention. The Examiner states that an affidavit or declaration by Applicants stating that the instant invention will be irrevocably and without restriction released to the public upon issuance of Letters Patent, is required to satisfy the deposit requirements.

7. In response to the Examiner's rejection as described in the preceding paragraph, I hereby declare that the *Leptospira fainei* strain WKID deposited with Australian Government Analytical Laboratories (AGAL) at 1 Suakin Street, Pymble, New South Wales 2073, Australia, under the provisions of the

Budapest Treaty on the International Recognition of the Deposit of Microorganism for the Purpose of Patent Procedure, and assigned AGAL Accession No. N95/69684, will be irrevocably and without restriction released to the public upon issuance of Letters Patent on the present application. I further declare that, during the pendency of the present application access to the deposited *L. fainei* strain WKID (AGAL N95/69684) will be afforded the Commissioner of Patents on request. I further declare that the deposit will be maintained with AGAL or other recognized public depository under the provisions of the Budapest Treaty for the enforceable life of Letters Patent issued on the present application, and that the deposit will be replaced if it ever should become inviable.

8. At paragraph 14 of the Office Action, the Examiner has rejected Claims 1-2, and 15-18 under 35 USC 102(a) as being anticipated by Perolat *et al* (EMBL U60594). The Examiner states that the entry in the EMBL database is described as a characterization and phylogenic analysis of *Leptospira fainei* species isolated from Australian pigs, said *L. fainei* being from the strain Hurstbridge having a 16S ribosomal RNA sequence of 1481 base pairs in length.

9. In response to this rejection by the Examiner, I firmly believe that the disclosure of the 16S rRNA gene sequence by Perolat (EMBL U60594) does not anticipate the claimed genus of bacteria that are serologically cross-reactive with *L .fainei* strain WKID (AGAL N95/69684) under 35 USC 102(a).

10. It is my understanding from the Office Action that 35 USC 102(a) reads as follows:

> "A person shall be entitled to a patent unless -
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent."

In this respect, the Perolat disclosure was the consequence of my inventive work, as partially evidenced by the fact that I am a co-author of that disclosure The remaining authors of the citation were my scientific collaborators in 1994, however the concept and reduction to practice of the 16S rRNA disclosed in the citations were either produced in my laboratory before this date, or alternatively, were the product of my direct supervision.

11. More particularly, the gene sequence contained in the citation is the 16S rRNA gene sequence of *L. fainei* strain BUT6, and not strain WKID (AGAL Accession No. N95/69684). Partial sequencing of serovar hurstbridge (bases 51-199) was performed by my laboratory during March 1994. It was on the basis of this sequencing, as well as the result of pathogen-specific PCR, that

the first four isolates of bacteria belonging to the new serological grouping described as "serovar hurstbridge" were partially characterized. The similarity to *L. fainei* serovar lyme was also deduced from this partial sequence. Sequencing of bases 1-1481 of the gene was completed in June 1996, by Maria Serrano, an Honours student supervised by myself and Dr Ben Adler, of Monash University, Victoria, Australia. This sequence was the sequence submitted to GENBANK on 12 June 1996 and subsequently assigned EMBL Accession No. U60594. A copy of the sequence as submitted and confirmed by GENBANK is affixed hereto as Exhibit II. Comparison of records of the 1996 Serrano sequencing with the Perolat *et al* citation provides no evidence that Perolat or his Pasteur Institute colleagues ever sequenced *L. fainei* strain BUT6 independently, or that they ever sequenced *L. fainei* strain WKID (AGAL N95/6984) at all. The same portion of the gene was sequenced by Serrano *et al* and by Perolat *et al*. The technical details given by Serrano are more complete, but the Perolat *et al* published details appear to be a simplification of these.

12. Nor do Perolat *et al* mention or suggest any serological cross-reactivity to *L. fainei* strain WKID (AGAL N95/69684).

13. For the foregoing reasons I do not believe that the 16S rRNA gene sequence disclosed by Perolat *et al* (EMBL U60594) was described before my invention of this sequence.

14. At paragraph 15 of the Office Action, the Examiner has rejected Claims 1-2 and 15-18 under 35 USC 102(b), as being anticipated by Hookey (EMBL Z21634). The Examiner states that the entry in the EMBL database is described as a phylogeny of *Leptospira* and related spirochetes, wherein the 16S rRNA sequence of *Leptospira inadai* strain Lyme is disclosed, thereby teaching an isolated pathogenic Leptospira bacterium as required by the claims.

15. As a scientist having considerable skill as a bacteriologist, particularly in relation to the serology of Leptospires, I do not consider that the disclosure of a single rRNA sequence from serovar lyme could possibly be relevant, let along anticipate, Leptospires that are serologically cross-reactive with *L. fainei* strain WKID (AGAL N95/69684). Serovar lyme was the first serovar representing *L. inadai*. However, several serovars within the species are now recognized (see Faine *et al* (1999) "*Leptospira* and Leptospirosis, 2nd edition p194). Those serogroups within which the known serovars of *L. inadai* are placed include serogroup Lyme (serovar lyme), and serogroups Canicola, Icterohaemorrhagie, Javanica, Manhao, Shermani and Tarassovi. Each of these serogroups is unrelated serologically to serovar hurstbridge. As explained at page 43 of the specification, I sent one of the first isolates of serovar hurstbridge to the Leptospirosis Reference Library in Brisbane, Australia, in February 1994 to determine its serological cross-reactivity to

other Leptospires. The report, dated March 3 1994 stated that "Culture was sero-negative to our main panel of serovars". The isolate was later tested against antisera to all 23 available serogroups at the Pasteur Institute in Paris. In both cases, antiserum to serovar lyme was part of the panel tested, as were antisera to the six other serogroups listed above. However, no serological cross-reactivity between serovar hurstbridge and serovar lyme was ever detected.

16. Moreover, it is unlikely that a skilled bacteriologist would even be in a position to determine the serological cross-reactivity of a Leptospire from the mere disclosure of the 16S rRNA gene sequence of a single isolate, such as, for example, the teaching by Hookey *et al* (EMBL Z21634). In contrast to the genetic classification of Leptospires based on 16S rRNA gene sequence as taught by Hookey *et al* (EMBL Z21634) or Perolat *et al* (EMBL U60594), the serological classification of Leptospires is based upon agglutinating epitopes of the surface lipopolysaccharide (LPS) of the various isolates. Thus, whilst serovar lyme and serovar hurstbridge possess some identity in their rRNA gene sequences, such information is not predictive of an antigenic relationship. Accordingly, mere disclosure of a single 16S rRNA gene sequence cannot anticipate, in my opinion, a claim to isolated Leptospires that are serologically cross-reactive to strain WKID (AGAL N95/69684).

17. For the foregoing reasons, I disagree with the Examiner's conclusion that Hookey *et al* anticipates our claim to Leptospires that are serologically cross-reactive with the deposited strain.

18. At paragraph 16 of the Office Action, the Examiner has rejected Claims 1-6 and 10 under USC 102(b), as being anticipated by Perolat *et al.*, (Abstracts). The Examiner states that Perolat *et al.*, teach molecular and phenotypic characterization of Hurstbridge strains as a new genomic species of pathogenic *Leptospira*, that grows at a temperature in the range of 13° -30°C which is in between the pathogenic and saprophytic species, and on 8-azaguanine, thereby providing evidence of a serovar designated Hurstbridge. Accordingly, the Examiner considers that Perolat *et al.*, (Abstract) teaches the invention as claimed.

19. As a scientist having considerable skill in the art, I firmly believe that the abstract by Perolat *et al* (1996) does not enable the isolation and subsequent identification of the claimed genus of serologically cross-reactive Leptospires to strain WKID (N95/69684). Perolat *et al* (1996) merely teach the isolation of leptospiral bacteria having the following characteristics:

- Failure to agglutinate significantly with antisera to serovars representative of 23 recognized pathogenic serogroups;
- Failure of antisera raised against the isolate to agglutinate any of these 23 recognized pathogenic serovars;

- Failure of the isolate to cross-agglutinate with serovars representative of recognized saprophytic serogroups.

Any number of different leptospires from serogroups other than those currently recognized could meet these criteria.

20. Moreover, Perolat *et al* (1996) do not provide an enabling disclosure of the conditions used to isolate the deposited strain WKID (AGAL N95/69684) and other serologically cross-reactive isolates as described at page 41, line 19, to page 42, line 24, of the specification.

21. As to the reference by Perolat *et al* (1996) to the strain BUT6, in the second paragraph of the citation, this reference is made only in respect of the similarity between the rRNA gene sequence of strain BUT6 and the reference strains of validated genospecies: *L. interrogans*, *L. borgpetersenii*, *L. inadai*, *L. kirschneri*, *L. meyeri*, *L. noguchii*, *L. santarosai*, *L. weilii*, *L. biflexa* and *T. parva*. There is no specific teaching by Perolat *et al* (1996) of the deposited strain WKID (AGAL N95/69684) or the genus of serologically cross-reactive Leptospires thereto. As stated *supra*, such genetic relationship is not predicative of serological cross-reactivity.

22. Moreover, the strain BUT6 as described in the present application, at page 4, line 4, of the specification, autoagglutinates strongly, and cannot be used to determine serologically cross-reactive isolates by microscopic agglutination test (MAT). This observation was made first in my laboratory, and later by my collaborators at Monash University. In contrast, the deposited strain WKID (AGAL N95/69684) was not found to autoagglutinate to any major extent. All subsequent serological studies on serovar hurstbridge have, therefore, been performed using strain WKID. The reason for autoagglutination of some leptospiral strains is unknown.

23. For the foregoing reasons, it is not possible to conclude that what Perolat *et al* (1996) describe as serovar Hurstbridge, or strain BUT6 for that matter, is antigenically cross-reactive to the deposited strain WKID (N95/69684) of the present application. I firmly believe that possession of the deposited strain is the only basis on which such a conclusion could be reached, however Perolat *et al* (1996) is a mere paper disclosure with no tangible enabling support in the form of a viable bacterial isolate.

24. I also consider that Perolat *et al* (1996) do not enable a skilled person to determine a serological grouping of leptospires based on cross-agglutination with the deposited strain WKID (N95/69684), because they merely described some characteristics of a single isolate. In contrast, a serological grouping (i.e. serovar or serogroup) requires knowledge of more than a single isolate. In the present application, the serogroup that is cross-reactive to the deposited strain WKID (AGAL N95/69684) was determined based upon the

provision of five isolates (see page 45 of the specification). Those skilled in the art are aware that a single isolate as taught by Perolat *et al* (Abstract) is insufficient to determine a serological grouping.

25. For the foregoing reasons, I believe that Perolat *et al* (Abstract) does not anticipate leptospires that are serologically cross-reactive to strain WKID (AGAL N95/69684).

26. At paragraph 17 of the Office Action, the Examiner has rejected Claims 7 and 9 under 35 USC 103(a) as being unpatentable over Perolat *et al.*, (EMBL U60594) or Hookey (EMBL Z21634) or Perolat *et al.*, (Abstracts) in view of Chappel *et al.*, (Manipulating Pig Production). The Examiner states that it would have been obvious at the time of the invention to take the knowledge of human infection by *Leptospira* bacterium as taught by Chappel *et al.*, (Manipulating Pig Production) and apply that knowledge to the known *Leptospira* bacteria as taught by Perolat *et al.*, (EMBL U60594) or Hookey (EMBL Z21634) in view of Perolat *et al.*, (Abstracts), because Chappel *et al.*, (Manipulating Pig Production) teaches that human *Leptospira* infection is an important field of research.

27. At paragraph 18 of the Office Action the Examiner has rejected Claims 8, 11-14 under USC 103(a) as being unpatentable over Perolat *et al.*,(EMBL U60594) or Hookey (EMBL Z21634) or Perolat *et al.*, (Abstract) in view of Chappel *et al.*, (Pig Research Report). The Examiner states that Chappel *et al.*, (Pig Research Report) teach that infection of *Leptospira* can cause infertility, abortions, still births and is associated with seasonal infertility (page 3); that serovars can also cause early embryonic loss, however vaccination against the *bratislava* serovar can improve the farrowing rate in herds (page 6); that isolates used in the study were grown at 13°C in the present of 8-azaguanine (page 4), and that a partial sequence of the 16S ribosomal RNA gene was obtained and sequence homology was compared (page 4); that other research methods detect Leptospira from bovine urine (page 5); that a previously undiscovered leptospiral serovar which is a member of the pathogenic species *Leptospira inadai* and a serovar within the *L. inadai* (page 5); and that several pigs had the Hurstbridge serovar (page 13). The Examiner concludes that no more than routine skill would have been required to use known infection capabilities of *Leptospira* as taught by Chappel *et al.*, (Pig Research Report) with the isolated *Leptospira* bacterium of Perolat *et al.*, (EMBL U60594) or Hookey (EMBL Z21634) or Perolat *et al.*, (Abstracts) because Chappel *et al.*, (Pig Research Report) teaches that reproductive problems are well known to be associated with *Leptospira* infections in pigs and bovines.

28. At paragraph 19 of the Office Action the Examiner rejects Claims 5-8, 10, 12, and 124-126 under 35 USC 103(a) as being unpatentable over Perolat *et al.*, (EMBL U60594) or Hookey (EMBL Z21634) or Perolat *et al.*, (Abstracts) in

view of Haake *et al.* The Examiner states that Haake *et al.*, (US Patent 5,643,754) teaches that leptospirosis is a widespread zoonotic disease caused by pathogenic strains of Leptospira that are capable of infecting most mammalian species (col. 1 lines 20-25); that infection in livestock causes loss due to abortion, stillbirth, infertility, decreased milk production and death (col. 1 lines 27-30); that Leptospira proteins may be comprised in pharmaceutical compositions useful for inducing immune responses in animals (col. 7 lines 30-34); and that preparations include sterile or aqueous or non-aqueous solutions, suspension, emulsions and other like examples (col. 7 lines 45-50). The Examiner considers that it would have been obvious at the time of applicants invention to combine Leptospira with a pharmaceutically acceptable diluent as taught by Haake *et al.*, with the bacterium of Perolat *et al.*, (EMBL U60594) or Hookey (EMBL Z21634) or Perolat *et al.*, (Abstracts) because Haake *et al*, states that such compositions may induce an immune response in animals.

29. For the reasons discussed hereinabove, I do not consider that Perolat *et al* (EMBL U60594) or Perolat *et al* (Abstract) or Hookey *et al* (EMBL Z21634) provide a sufficient disclosure to enable a person of ordinary skill in the art to isolate a leptospire bacterium that is serologically cross-reactive to the deposited strain WKID (N95/69684). I also do not consider that these citations would collectively enable such isolates or antigenic determination, because no citation provides a bacterial isolate having the low auto-agglutination characteristics of the deposited strain. Additionally, as stated hereinabove, it is not possible to determine a serological grouping of leptospires from 16S rRNA gene sequence data or the provision of a single isolate, as taught by these citations. Accordingly, in contrast to the Examiner's conclusion, I do not consider that the combination of Perolat *et al* (EMBL U60594) or Perolat *et al* (Abstract) or Hookey *et al* (EMBL Z21634) with the disclosure by Chappel *et al* (Manipulating Pig Production) or alternatively, Chappel *et al* (Pig Research Report) or alternatively, Haake *et al* (USSN 5,643,754), would render obvious a bacterium that is serologically cross-reactive to strain WKID (AGAL N95/69684) with or without a pharmaceutically acceptable carrier or diluent, and which is capable of infecting humans and/or causing leptospirosis in a human or causing reproductive disease in a human, or animal subject.

30. I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that wilful false statements and the like so made are punishable by fine or imprisonment or both, under Section 1001 of Title 18 of the United States Code, and that such wilful statements, may jeopardise the validity of the application or any patent issuing therefrom.

DATED this TWENTY-SIXTH day of SEPTEMBER, 2001.

RJ Chappel

Roderick J. Chappel